UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/135,238	08/17/1998	GARRY P. NOLAN	A-65635-1/DJ	9052

24353 7590 11/06/2002

BOZICEVIC, FIELD & FRANCIS LLP
200 MIDDLEFIELD RD
SUITE 200
MENLO PARK, CA 94025

EXAMINER
SHUKLA, RAM R

ART UNIT	PAPER NUMBER
1632	20

DATE MAILED: 11/06/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/135,238	NOLAN ET AL.	
	Examiner	Art Unit	
	Ram R. Shukla	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *58-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *58-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The request filed on 5-6-02 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/135,238 is acceptable and a CPA has been established. An action on the CPA follows.

2. Amendment filed 8-21-02 has been entered.

3. New claims 58-66 have been entered and are pending in the instant application.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 58-66 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claimed invention encompasses any polypeptide that specifically binds to a TOSO protein that has at least about 90% sequence identity to SEQ ID NO 2, antibodies that bind to SEQ ID NO 2, antibodies that modulate (increase or decrease) the biological function of TOSO and antibodies that are directed against the extracellular or cytoplasmic domain of TOSO. However, the specification does not disclose any polypeptide that specifically binds to TOSO or any antibody that binds or recognizes TOSO or has any function.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, the specification does not describe structure of any TOSO binding protein or any TOSO binding antibody.

The specification does not provide any disclosure as to what would have been the sequence structure of any claimed polypeptide.

Next, then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence). Again, no identifying characteristics have been described for any antibody. For example, while the claims recite an antibody that increases or decreases TOSO activity, the specification does not provide any other characteristics of any such antibodies. While the claims describe 90% sequence recite sequence identity of the TOSO protein, no description is provided as to what characteristics the antibodies would have. It is noted that while claims 61-63 recite function of the antibody, in the absence of description of their structure, an artisan would not know what was the structure of the claimed polypeptide or antibodies.

This limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of any polypeptide or antibody at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 58-60, 64 and 65 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody that binds to the TOSO protein of SEQ ID NO 2 or an antibody the is directed against the extracellular domain or cytoplasmic domains of SEQ ID NO 2, does not reasonably provide enablement for any protein that binds to TOSO of SEQ ID NO 2 or to a TOSO protein that has 90% sequence identity to SEQ ID NO 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is

most nearly connected, to make or use the invention commensurate in scope with these claims.

Claims 61-63 and 66 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue".

Claimed invention encompasses any polypeptide that specifically binds to a TOSO protein that has at least about 90% sequence identity to SEQ ID NO 2, antibodies that bind to SEQ ID NO 2, antibodies that modulate (increase or reduces or eliminates) the biological function of TOSO and antibodies that are directed against the extracellular or cytoplasmic domain of TOSO, and a method of treating any apoptosis related condition in a mammal by administering an anti-TOSO antibody.

The specification as filed is not enabling for the claimed invention because the specification as filed does not provide sufficient guidance as to what would be considered a TOSO protein, how would an artisan have made a polypeptide that binds to TOSO protein and used it or would have produced and used an anti-TOSO antibody for the intended utility and an artisan of skill would have required extensive experimentation to practice the claimed invention and such experimentation would have been undue since the specification does not provide

sufficient guidance as to how to make and use the claimed invention and the art of treating a disease with anti-TOSO antibody was unpredictable. If an artisan could not decide what was a TOSO protein, how would an artisan be able to produce an anti-TOSO antibody?

Next, the specification does not teach how to isolate a protein that binds to TOSO of SEQ ID NO 2 or a TOSO protein that has 90% sequence identity to SEQ ID NO 2. It is noted that the specification does not provide any guidance as to how to make a protein that binds to any TOSO protein, for example, how will a TOSO binding polypeptide be isolated or identified, what assay will be used to determine that a given polypeptide binds to TOSO? Next the issue is, how would an artisan have made any TOSO protein that has 90% sequence identity to SEQ ID NO 2 for making polypeptides that binds to such TOSO proteins? The protein of SEQ ID NO 2 is a 390 amino acid protein, which means an artisan could alter up to 39 amino acids to make proteins encompassed by the claimed invention. However, the specification does not teach as to which 39 amino acids (consecutive or at random) will be changed so that the resultant protein retains its function. It is noted that at the time of the invention, it was not routine in the art to randomly alter 10% amino acids of a protein and maintain the function of the starting protein. It is recognized in the prior art that the function of a protein depends on the sequence of its amino acids in a certain pattern, conformation of the protein due to the amino acid sequence, and the functional properties of the different parts of the protein (see second paragraph in Rudinger J in Peptide Hormones. Editor Parsons JA. Pages 1-7, 1976, University Park Press, Baltimore). Rudinger further add, "The significance of particular amino acids and sequences for different aspects of biological activity can not be predicted *a priori* but must be determined from case to case by painstaking experimental study" (see conclusion on page 6). The specification does not teach which changes in the amino acid sequences of the SEQ ID NO 2 would retain the function of the TOSO protein and therefore, such protein could be used for producing antibodies or for identifying binding proteins. Particularly, if the amino acid sequence was changed by 10 percent, it is not clear whether the resultant protein will retain the function of the starting protein, if not how would the protein

have been used for its intended utility. The specification does not teach how to use a protein, which was derived from the protein of SEQ ID NO 2 but did not have the function of the starting protein. Alternatively, the specification does not teach how make a protein in which 10% amino acids would have been changed but the protein would have retained the function of the starting protein. As set forth in *In re Fisher,* 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

Next regarding the invention of claims 61-63 and 66, it is noted that the specification is not enabling for the invention of these claims.

The specification is not enabling for the claimed invention because in addition to the issues raised and reasons set forth above, neither the specification nor the prior art teaches as to whether anti-TOSO antibody would have treated any condition related to apoptosis in any mammal in vivo or would have modulated the biological function of TOSO protein in vivo or in vitro because neither the art nor the specification teaches treating any apoptosis related condition with anti-TOSO antibody and the art of antibody therapy was unpredictable at the time of the invention and the specification as filed does not provide sufficient guidance, evidence and working examples for an artisan to have practiced the claimed method without undue experimentation.

First, as noted in the specification, TOSO is expressed in T cell derived cell lines but not in other cells (lines 23-25, page 45), if so will TOSO modulate apoptosis in any and all cells, particularly when effect of TOSO is through T cell receptor dependent signal transduction (see figure 10). The specification does not provide any guidance as to whether TOSO would affect apoptosis in any and all

cells in the absence of the signal transduction pathway wherein TOSO works. Next the specification does not provide any guidance whether the TOSO antibody would have been administered to only those cells, which are known to express TOSO cells, or it would have been delivered to all the cells of the body. Furthermore, there is nothing on the record to teach whether administration of TOSO antibody to cells where it is normally not expressed would have affected the normal physiology of the cells or would have induced apoptosis in normal cells. Additionally, the specification does not provide any guidance whether anti-TOSO antibody would have inhibited or activated apoptosis by any method such as by tumor suppressor genes, such as P53 or bcl. Next, the specification does not provide any guidance as to whether anti-TOSO antibody provided to a cell in vivo, would have affected apoptosis.

It is noted that the prior art does not provide any guidance as to what would be the effect of TOSO or anti-TOSO antibody on apoptosis in vivo. There is only one article published on TOSO, which is by the applicants group and which describes cloning and characterization of TOSO (Hitoshi Y et al. Immunity 8: 461-471, 1998). In this article, inventors have disclosed that TOSO does not inhibit apoptosis by different mechanisms, such as staurosporine-induced apoptosis or ceramide induced apoptosis. Additionally, TOSO did not have apoptotic effects downstream or at the level of capase-3. Likewise, TOSOS did not mediate BCL-Xl or BCL-2 related apoptotic effects (see last paragraph in column on page 468). This indicates that TOSOS would not affect apoptotic effects of a cell where apoptosis was induced by different mechanism. Furthermore, Hitoshi et al note that TOSO may be responsible for down-regulating Fas-mediated apoptosis pathway of activated T cells, however, it is not clear as to when given how would anti-TOSO antibody would discriminate between apoptosis of activated T cells that is normal versus apoptosis of activated T cells protein that may be disease related and needed therapeutic correction and the specification does not provide any guidance regarding this issue.

It is noted that the only reference to an anti-TOSO antibody in the specification is present on page 12, lines 15-25, page 13, lines 1-7 and page 28,

lines 17-28, however, these sections of the specification only describe or define terms and do not provide any description as to how the treatment method using anti-TOSO antibody would have been carried out. While it would have been routine to produce antibodies, it was not routine to treat any apoptosis related condition with anti-TOSO antibody. For example, there is no description of as to what regions of TOSO could be used to produce antibody that would treat a disease or increase TOSO activity or as to how would an anti-TOSO antibody would have been administered or what doses would have been used. Additionally, the specification does not teach as to what disease could be treated by administering TOSO antibody. Regarding claims 61-63, since the only disclosed utility for these would be treatment, the specification is not enabling as discussed above. While applicants list diseases that can be treated using TOSO protein, the specification does not provide any guidance as to what specific diseases would be treated by increasing the biological activity with TOSO antibody or how would an artisan make an antibody that would increase the biological function of TOSO. The specification does not teach as to how and in what form the TOSO antibodies will be administered for treating any apoptosis related condition. At the time the invention was made, the claimed antibodies were not routinely used for the treatment of any disease or condition. The specification lacks guidance by way of general methods or working examples which teach an "effective amount" of antibody which would be used for this purpose. Lack of working examples is given added weight in cases involving an unpredictable and undeveloped art, such as immunotherapy using antibody. It is unpredictable whether the claimed antibody, would have resulted in treating any disease because the specification has not disclosed a link or nexus between the generation of anti-TOSO antibodies and any condition and its use in the treating any disease. At the time of the invention, it was not routine in the art to treat any disease with antibodies. Various factors governing the success of antibody therapy are: target antigen and designing the antibody, pharmacokinetics of the antibody in vivo, reaching the target, binding of the antibody to the target and antibody clearance (see Russell et al. Principles of antibody therapy. British Medical Journal.

305:424-429, 1992; Mehren et al. Monoclonal anti-body based therapy. Current Opinion in Oncology. 8:493-498, 1996). The specification does not provide any guidance as to how would an artisan have addressed these issues regarding treatment of any apoptosis related condition using TOSO antibody. Accordingly, there is no objective basis upon which the skilled artisan would reasonably be able to determine or predict an amount of the claimed antibody effective for its intended use. Therefore, undue experimentation would be required to make and use the invention.

Accordingly, the specification is not enabling for the claimed method of treatment by modulating apoptosis related conditions. In the absence of any guidance in the prior art on the role of TOSO in vivo, an artisan has to depend on the teachings in the specification, however the specification does not provide sufficient guidance as to how an artisan would have addressed the issues of general nature and related to antibody therapy method as discussed above.

In conclusion, the specification as filed is not enabling for the claimed method commensurate with the scope of the claims and therefore, limiting the claimed invention to an antibody that binds to the TOSO protein of SEQ ID NO 2 or an antibody the is directed against the extracellular domain or cytoplasmic domains of SEQ ID NO 2 is proper.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the

application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

9. Claims 58-60 and 64-65 are rejected under 35 U.S.C. 102(e) as being anticipated by Wu et al (US Patent 6,111,515, dated 9-5-00, effective filing date 8-25-1997).

Wu et al teach a polypeptide named PIGRL-1 a member of immunoglobulin gene superfamily. The amino acid sequence of the protein (SEQ ID NO 2) of the patent has 100% sequence identity with the sequence of SEQ ID NO 2 of the instant application. In column 15, lines 34-66, the patent disclose antibodies against the PIGRL-1 polypeptides (full length or fragments). Accordingly, the claimed invention is anticipated by Wu et al.

10. No claim is allowed.

When amending claims, applicants are advised to submit a clean version of each amended claim (without underlining and bracketing) according to § 1.121(c). For instructions, Applicants are referred to http://www.uspto.gov/web/offices/dcom/olia/aipa/index.htm.

Applicants are also requested to submit a copy of all the pending/under consideration claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for this Group is (703) 308-4242. Any inquiry of a general nature, formal matters or relating to the status of this

application or proceeding should be directed to the Dianiece Jacobs whose telephone number is (703) 305-3388.

Ram R. Shukla, Ph.D.

RAM R. SHUKLA, PH.D
PATENT EXAMINER